A combination of TH-302 and radiation reduced human pancreatic tumor growth in hypoxic xenografts

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A combination of the prodrug TH-302 and radiation may provide an effective treatment strategy for pancreatic cancer, according to preclinical results presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held here June 18-21.

"We found that the combination of TH-302 and ionizing radiation reduced pancreatic tumor growth in hypoxic xenografts," said Ines Lohse, Ph.D., a postdoctoral fellow at the Ontario Cancer Institute at the Princess Margaret Hospital in Toronto, Canada. "The response we observed depended on the magnitude of tumor hypoxia and the tumor growth rate.

"We have previously shown that hypoxia in our patient-derived pancreatic tumor models correlates with aggressive growth and a high metastatic potential, meaning if a tumor shows high levels of hypoxia, it will grow faster and is more likely to metastasize," Lohse said.

All solid tumors contain areas of low oxygen tension (that is, regions of hypoxia). Cancer cells in these areas are less responsive to standard cancer chemo- and radiotherapy. Researchers hypothesize that drugs that can specifically target these regions will increase primary tumor treatment responses and prevent tumor recurrence and metastasis. One strategy under investigation is to use therapies that are toxic only under

hypoxic conditions, for example, prodrugs that are converted to their active form by hypoxia.

In preclinical models of pancreatic cancer, Lohse and colleagues tested TH-302, a tumor-selective, hypoxia-activated, cytotoxic prodrug that specifically targets the areas of extreme hypoxia found in solid tumors. Using seven patient-derived pancreatic tumor models grown in immune-compromised mice, they assessed the efficacy of treatment with TH-302 alone, ionizing radiation alone or a combination of the two, wherein the mice received three 50 mg/kg doses of the drug and ionizing radiation on three consecutive days.

The combination treatment reduced tumor growth in high and medium hypoxic xenografts; however, the combination had little effect on tumor growth in low- or nonhypoxic implants. Treatment efficacy depended on the extent of tumor hypoxia and tumor growth rate.

"We were expecting that hypoxia would be a strong predictor of treatment efficacy," Lohse said. "But in our models, we actually showed that hypoxia is not the only predictor. Tumor growth rates are equally important in predicting treatment efficacy.

"Our results strongly support the ongoing clinical trials of TH-302," said Lohse. "In these trials, TH-302 is being tested in combination with chemotherapy, and one combination has, in fact, been recently reported to prolong progression-free survival in patients with advanced pancreatic cancer. We hope that our data might lead to TH-302 being tested in combination with ionizing radiation as an alternative treatment option for pancreatic cancer."

More information:

Abstract

Targeting Tumor Hypoxia in Patient-Derived Pancreatic Xenografts Using TH-302. Ines Lohse, Joanna Rasowski, PinJiang Cao, Emin Ibrahimov, Melania Pintille, Ming S. Tsao, Richard Hill, David W. Hedley. Ontario Cancer Institute / Princess Margaret Hospital, Toronto, ON, Canada.

All solid tumors independent of their origin contain areas of low oxygen tension. It is well established that tumor hypoxia induces an epigenetic selection for cancer cells that survive the hostile tumor microenvironment. Tumors resistant to hypoxia are generally more aggressive and less responsive to cancer therapy than hypoxia-sensitive tumors. We have recently shown that high levels of hypoxia in patient-derived pancreatic cancer xenografts correlate with both increased metastatic potential and high proliferation. The tumor selective hypoxia-activated cytotoxic prodrug TH-302 specifically and selectively targets extreme hypoxia found in solid tumors and is therefore believed to not only increase the treatment response of the primary tumor but also prevent tumor recurrence and metastasis. The clinically validated warhead functions as an alkylator that kills dividing as well as non-dividing tumor cells while designed to be inactive and non-toxic in normal tissues. Several clinical trials are currently ongoing to investigate the effect of TH-302 on various cancers in combination with established chemotherapeutics. We used 7 patient-derived xenograft models to examine the efficiency of the hypoxia-activated drug TH-302 in pancreatic tumors. Mice received a chronic treatment with TH-302 alone, IR alone or the combination treatment; where TH-302 treated mice received 3 doses of 50mg/kg TH-302 and ionizing radiation (IR) treated mice received 2Gy on 3 consecutive days. TH-302 specifically targeted the hypoxic zone in the xenograft models. Additionally, TH-302 treatment induced DNA damage in tumor tissue adjacent to the hypoxic zone which is consistent with the previously demonstrated bystander effect of TH-302. In the primary patient-derived xenograft models treatment with TH-302 in combination with IR reduced tumor growth in

high and medium hypoxic xenograft models, while having little impact on tumor growth in low or non hypoxic models. Furthermore, our results showed that TH-302 treatment efficiency depended on the extent of tumor hypoxia and the tumor growth rate. While showing high treatment efficiency even as a single agent in fast-growing hypoxic models, TH-302 treatment had little effect on tumor growth in a hypoxic model that displayed slow growth rates. Together, these findings demonstrate that the combination of radiation therapy and TH-302 may provide an effective treatment strategy for pancreatic cancer patients.

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